
Timothy syndrome is associated with activity-dependent dendritic retraction in rodent and human neurons.

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Authors: Jocelyn F Krey, Sergiu P Pasca, Aleksandr Shcheglovitov, Masayuki Yazawa, Rachel Schwemberger, Randall Rasmusson, Ricardo E Dolmetsch

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Public Summary:

L-type voltage gated calcium channels have an important role in neuronal development by promoting dendritic growth and arborization. A point mutation in the gene encoding L-type calcium channel CaV1.2 causes Timothy syndrome, a neurodevelopmental disorder associated with autism spectrum disorders (ASDs). We report that channels with the Timothy syndrome mutation cause activity-dependent dendrite retraction in rat and mouse neurons and in induced pluripotent stem cell (iPSC)-derived neurons from individuals with Timothy syndrome. Dendrite retraction was independent of calcium entrance through the mutant channel, was associated with ectopic activation of RhoA GTPase and was inhibited by increased expression of the channel-associated GTPase Gem. These results provide insights into the cellular basis of Timothy syndrome and other ASDs.

Scientific Abstract:

L-type voltage gated calcium channels have an important role in neuronal development by promoting dendritic growth and arborization. A point mutation in the gene encoding Ca(V)1.2 causes Timothy syndrome, a neurodevelopmental disorder associated with autism spectrum disorders (ASDs). We report that channels with the Timothy syndrome alteration cause activity-dependent dendrite retraction in rat and mouse neurons and in induced pluripotent stem cell (iPSC)-derived neurons from individuals with Timothy syndrome. Dendrite retraction was independent of calcium permeation through the mutant channel, was associated with ectopic activation of RhoA and was inhibited by overexpression of the channel-associated GTPase Gem. These results suggest that Ca(V)1.2 can activate RhoA signaling independently of Ca(2+) and provide insights into the cellular basis of Timothy syndrome and other ASDs.

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